LISTING OF THE CLAIMS:

1. (original) A method for identifying and/or obtaining a modulator of a rhomboid polypeptide, which method comprises:

(a) contacting a rhomboid polypeptide and a substrate polypeptide in the presence of a test compound and one or more non-rhomboid proteases,

wherein said substrate polypeptide comprises a core domain which has a rhomboid cleavable TMD sequence linked to an upstream tag sequence, the core domain sequence not being susceptible to cleavage by the one or more non-rhomboid proteases, and;

(b) determining the presence or amount in said medium of a soluble polypeptide fragment comprising said tag sequence.

2. (original) A method according to claim 1 wherein said Rhomboid polypeptide and said substrate polypeptide are co-expressed in a cell.

3. (original) A method according to claim 2 wherein the cell is a mammalian cell.

4. (previously presented) A method according to Claim 1 wherein the presence of the soluble substrate polypeptide is determined by;

(a) contacting said medium with an specific binding member which binds to said tag sequence, and

(b) determining binding of soluble polypeptide fragment to said binding member.

5. (original) A method according to claim 4 wherein said specific binding member is immobilised.

6. (original) A method according to claim 5 wherein said specific binding member is an antibody.

7. (original) A method according to claim 6 wherein said antibody is imrnobilised on the surface of microtitre plate.

8. (previously presented) A method according to Claim 1 wherein the substrate polypeptide comprises an extracellular detectable label.

9. (original) A method according to claim 8 wherein the label is secreted alkaline phosphatase.

10. (previously presented) A method according to claim 8 wherein the binding of said polypeptide fragment to said anti-tag antibody is detected by determining the amount of said label bound to the antibody.

11. (original) A method according to claim 10 wherein the amount of said label is determined by contacting said label with a reporter molecule which produces a signal in the presence of said label, and measuring said signal.

12. (original) A method according to claim 11 wherein the signal is light emission.

13. (previously presented) A method according to Claim 1 wherein the tag sequence is positioned 10 amino acid residues or less upstream of said TMD in said core domain.

14. (previously presented) A method according to Claim 1 wherein the tag sequence consists of 30 amino acids or less.

15. (previously presented) A method according to Claim 1 wherein the tag sequence is $MRGS(H)_6$.

16. (previously presented) A method according Claim 1 wherein the rhomboid cleavage TMD rhomboid comprises a lumenal portion which has the same conformation within the membrane as Spitz residues 140-144.

17. (original) A method according to claim 16 wherein the rhomboid cleavable TMD has a lumenal portion which comprises or consists of Spitz residues 140-144 (IASGA) .

18. (previously presented) A method according to claim 16 wherein the rhomboid cleavable TMD is a rhomboid ligand TMD.

19. (original) A method according to claim 18 wherein the rhomboid cleavable TMD is the Spitz TMD.

20. (previously presented) A method according to Claim 1 wherein the substrate polypeptide comprises a cytoplasmic domain, said domain comprising the cytoplasmic domain of TGFα.

21. (previously presented) A method according to Claim 1 wherein the substrate polypeptide comprises a cytoplasmic domain, said domain comprising the cytoplasmic domain of thrombomodulin.

22. (previously presented) A method according to Claim 1 wherein the Rhomboid polypeptide has a sequence shown in Table 1.

23. (original) A method according to claim 22 wherein the Rhomboid polypeptide is selected from the group consisting of Drosophila Rhomboid 1, Drosophila Rhomboid 2, Drosophila Rhomboid 3, Drosophila Rhomboid 4, Human RHBDL-1, Human RHBDL-2 and Human RHBDL-3, E. coli glgG, B. subtilis ypqP, P. stuartii A55862 gene product, P. aeruginosa B83259 gene product, S. cerevisiae YGRlOlw and S. cerevisiae YPL246c.

24. (previously presented) A method according to Claim 1 comprising identifying said test compound as a modulator of Rhomboid protease activity.

25. (original) A method according to claim 24 comprising isolating said test compound.

26. (original) A method according to claim 25 comprising synthesising and/or preparing said test compound.

27. (previously presented) A method according to claim 25 comprising modifying said compound to optimise the pharmaceutical properties thereof.

28. (previously presented) A method according to Claim 24 comprising formulating said test compound in a pharmaceutical composition with a pharmaceutically acceptable excipient, vehicle or carrier.

29. (previously presented) A modulator of Rhomboid protease activity obtained by a method of Claim 1.

30. (previously presented) A method of making a pharmaceutical composition comprising,

identifying a compound as a modulator of Rhomboid activity the method according to Claim 1,

synthesising, preparing or isolating said compound and admixing the compound with a pharmaceutically acceptable excipient, vehicle or carrier, and optionally other ingredients to formulate or produce said composition.

31. (original) A method according to claim 30 comprising modifying said compound to optimise the pharmaceutical properties thereof.

32. (previously presented) A method according to claim 30 comprising determining the activity of a Rhomboid polypeptide in the presence of said composition.

33. (original) A polypeptide which is proteolytically cleavable by a Rhomboid polypeptide, said polypeptide comprising an a core domain which has a rhomboid cleavable TMD sequence linked to an upstream tag sequence, the core domain sequence not being susceptible to cleavage by mammalian metalloproteases.

34. (original) A polypeptide according to claim 33 wherein the tag sequence is positioned 10 amino acid residues or less upstream of said TMD in said core domain.

35. (previously presented) A polypeptide according to claim 33 wherein the tag sequence consists of 15 amino acids or less.

36. (original) A polypeptide according to claim 35 wherein the tag sequence is $MRGS(H)_6$.

37. (previously presented) A polypeptide according Claim 33 wherein the rhomboid cleavage TMD rhomboid comprises a lumenal portion which has the same conformation within the membrane as Spitz residues 140-144.

38. (original) A polypeptide according to claim 37 wherein the rhomboid cleavable TMD has a lumenal portion which comprises or consists of Spitz residues 140-144 (IASGA) .

39. (previously presented) A polypeptide according to claim 37 wherein the rhomboid cleavable TMD is a rhomboid ligand TMD.

40. (original) A polypeptide according to claim 39 wherein the rhomboid cleavable TMD is the Spitz TMD.

41. (previously presented) A polypeptide according to Claim 33 wherein the substrate polypeptide comprises an extracellular domain, said domain comprising a detectable label.

42. (original) A polypeptide according to claim 41 wherein the label is secreted alkaline phosphatase.

43. (previously presented) A polypeptide according to Claim 33 wherein the substrate polypeptide comprises a cytoplasmic domain, said domain comprising the cytoplasmic domain of thrombomodulin.

44. (previously presented) An isolated nucleic acid encoding a chimeric polypeptide according to Claim 33.

45. (original) An expression vector comprising a nucleic acid according to claim 44.

46. (previously presented) A host cell comprising an expression vector according to claim 45.

47. (original) A host cell according to claim 46 further comprising an expression vector comprising a nucleic acid encoding a rhomboid polypeptide.

48. (original) A method for obtaining a cleavage product of a Rhomboid polypeptide, which method comprises:

(a) contacting a Rhomboid polypeptide and a substrate polypeptide and one or more non-rhomboid proteases, wherein said substrate polypeptide comprises a core domain which has a rhomboid cleavable TMD sequence linked to an upstream tag sequence, the core domain sequence not being susceptible to cleavage by the one or more non-rhomboid proteases, and;

(b) contacting said medium with an antibody which binds to said tag sequence, and

(c) isolating/purifying soluble polypeptide fragment bound to said antibody.

49. (original) A method according to claim 48 comprising sequencing the polypeptide fragment.